The Sole Remaining Claim Rejection under 35 U.S.C. 103 is in error.

Claims 34-42 and 62-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,395,253 to Levy et al. (Levy) in view of O'Hagan et al., WO 00/50006 (O'Hagan) and Van Nest, US Pub. No. 2001/0046967 (Van Nest).

As noted in MPEP 2143.01, obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. However, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *Id.*, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). As discussed in more detail below, the modification of the prior art that is required to arrive at the present would render the prior art modified unsatisfactory for its intended purpose. Accordingly, the outstanding rejection under 35 U.S.C. 103(a) is clearly erroneous.

All pending independent claims are directed to a method of producing a microparticle composition, which method comprises: (a) forming an emulsion comprising (i) a polymer selected from the group consisting of a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate, (ii) an organic solvent, (iii) a detergent and (iv) water; (b) removing the organic solvent from the emulsion to form a microparticle suspension; (c) either (i) subjecting the microparticle suspension to a filtration step to remove excess detergent such that about 10-90% of the total detergent in the resulting microparticle suspension is bound to the microparticles and the remainder is unbound or (ii) not subjecting the microparticle suspension to a step to remove excess detergent and the ratio of the detergent to the polymer being used is such that about 10-90% of the total detergent in the microparticle suspension is bound to the microparticles and the remainder is unbound; and (d) mixing a biologically active macromolecule with said microparticle suspension in which about 10-90% of the total detergent in the microparticle suspension is bound to the microparticles and the remainder is unbound *such that said biologically active macromolecule is adsorbed to microparticles in said suspension*.

In the final Office Action, the Examiner notes that that Levy discloses preparation of microspheres that contain DNA or RNA as the bioactive agent. Specifically, Levy is cited as preparing water-in-oil-in water double emulsion by using a condensing agent and a method that

comprises the steps of: (a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic phase; (b) dissolving a polyanionic bioactive agent (preferably a nucleic acid) in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield microspheres containing condensed polyanionic bioactive agent.

With regard to the claimed microparticle suspension, the Examiner argues that Levy teaches an emulsion, and present within an emulsion are microspheres that meet the limitation of the microparticle suspension. In particular, the Examiner urges that an emulsion is a "special type of suspension," and that the suspension of the microspheres in the emulsion meets the limitation of a microparticle suspension. The Examiner further argues that combining the liquid phases in Levy meets the mixing step presently claimed, and that adsorption of macromolecule onto the microspheres would take place when macromolecules and the microspheres are placed together so that the macromolecules are adsorbed onto the microspheres.

Applicant respectfully disagrees.

The claimed suspension is a microparticle suspension that is *created by removal of the organic solvent* from an emulsion that comprises polymer, organic solvent, detergent and water. This solvent removal step removes the liquid component from the organic phase of the emulsion and produces a suspension of polymeric microparticles. (Such polymeric microparticles may be, for example, collected by centrifugation and lyophilized. See paragraphs [0096] and [0099] of the instant specification.) The resulting suspension of polymeric microparticles is subsequently mixed with a biologically active macromolecule such that the biologically active macromolecule is adsorbed to the same.

The polymer and biologically active agent in Levy, on the other hand, are contacted with one another in a multiphase emulsion containing (a) an organic phase containing at least one polymer dissolved in a water-immiscible organic solvent; (b) a first aqueous phase containing a polyanionic bioactive agent dissolved in aqueous solution; and (c) second aqueous phase containing a condensing agent dissolved in aqueous solution. Note that all of these phases are liquid phases (the organic phase is converted into microspheres upon removal of the water-immiscible organic solvent).

Unlike the present invention, in which a bioactive agent is adsorbed *onto* polymer microparticles after solvent removal, in Levy the bioactive agent, condensing agent, and polymer are brought together prior to solvent removal to incorporate the bioactive agent *into* the microspheres.

As seen throughout Levy, the condensing agent is provided to ensure that the active agent is ultimately positioned *inside* the polymer microspheres. See Levy Title ("Microspheres containing condensed polyanionic bioactive agents and methods for their production"). See also, the Abstract, Field of the Invention, Background, Summary, and Detailed Description of Levy, all of which it entirely clear that the Levy has supplied the condensing agent specifically to improve the amount of DNA incorporated *within* the microspheres. For example, the Abstract reads (emphasis added): "The invention describes improved methods for *incorporating* nucleic acids *into* polymeric microspheres and/or nanospheres through the use of a condensing agent." The Background asserts that the condensation of the DNA facilitates entry of the DNA into the cells. Col. 2, lines 24-27. See also the Summary of the Invention at col. 4, lines 14-18 (emphasis added): "The efficiency of incorporation of the polyanionic bioactive agents *into the microspheres* is increased by using a condensing agent to condense the polyanionic bioactive agent during the manufacture of the microsphere." See further the Detailed Description at col. 5, lines 55-59 (emphasis added): "The invention is based, in part, on the discovery that adding a polycationic condensing agent to a polyanionic bioactive agent during the production of microspheres increases the efficiency with which the *bioactive agent is incorporated into the microspheres*."

MPEP 2143.01 clearly states: "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." The modification required to arrive at the present invention, *inter alia,* requires a biologically active macromolecule to be mixed with a microparticle suspension containing bound and unbound detergent, after solvent has been removed, such that the biologically active macromolecule is adsorbed to the microparticles in the suspension. Such a method step is completely at odds with a process like that described in Levy in which a condensing agent is used to incorporate as much bioactive agent as possible within the microparticles.

In the Office Action, the Examiner states that "adsorption of macromolecule onto the [liquid polymer phase] microspheres would take place when macromolecules and the

microspheres are placed together so that the macromolecules are adsorbed onto the microspheres". The Examiner has provided no support for this assertion and it is believed to be without basis. Indeed, as previously indicated, in Levy, a condensing agent is provided ensure that the active agent is ultimately positioned *inside* the polymer microspheres.

The Examiner recognizes that the process steps claimed and those of Levy are different, but argues that Levy involves "putting together the same components to arrive at the same product" and that "selection of any order of performing process steps is prima-facie obvious in the absence of new and unexpected results [*sic,* new **or** unexpected results--see MPEP 2144.04]."

Here, however, the different process steps in Levy and the present invention yield two fundamentally different products: (a) microspheres *into* which bioactive agent is incorporated using a condensing agent as taught by Levy and (b) microparticles with adsorbed bioactive agent *on* the surface as claimed.

Since condensation of the bioactive agent within a microsphere is fundamentally different from adsorption of the bioactive agent at the surface, none of the Examiner's discussion of the disclosure of detergent in Levy is even vaguely relevant, as adsorption is never contemplated by Levy.

O'Hagan is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion with macromolecules, and Van Nest is relied upon for teaching that polynucleotides may be delivered in vehicles such as liposomes or emulsions made with cationic lipids or polymers, such as 1,2-dioleoyl- l,2,3-trimethylammoniopropane (DOTAP), cetyltrimethylammonium bromide (CTAB) or polylysine. Such teachings, however, do not make up for the above noted deficiencies in Levy.

For at least the above reasons, it is respectfully submitted that Levy, O'Hagan and Van Nest do not support a *prima facie* case of obviousness against claims 34-44 and 58-76.